PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000825	03.06.2004	26.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/48, A61K9/28, A61K9/20, A61K9/50, A61K31/44, A61P1/04

Applicant
ODIDI, Isa

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/000825

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29, 30, 46-48 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 29, 30, 46-48 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-48
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-28, 31-45
	No:	Claims	29, 30, 46-48

2. Citations and explanations

see separate sheet

III Non establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 29, 30, 46-48 in present description relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Documents
The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 : EP 1 017 370 A (NYCOMED DANMARK A S) 12 July 2000 (2000-07-12)
D2 : WO 03/009846 A (UNIV MISSOURI) 6 February 2003 (2003-02-06)
D3 : US 2002/045646 A1 (PHILLIPS JEFFREY O) 18 April 2002 (2002-04-18)
D4 : US 6 489 346 B1 (PHILLIPS JEFFREY OWEN) 3 December 2002 (2002-12-03)

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

2) Novelty - Article 33 (1) and (2) PCT

2.1) D1 discloses an oral pharmaceutical composition based on modified release multiple units (such as pellets) which are packed in a unit dosage form. This composition comprises:
- a first NSAID-containing fraction of multiple units for quick release of the NSAID
- a second NSAID-containing fraction of multiple units in the form of coated delayed release multiple units. Proton pump inhibitors (PPI) are listed as further active drug substances, for which such a composition could prove valid.

In the examples 7-9 pellet cores were manufactured which comprised sodium bicarbonate, dibasic calcium phosphate as alkaline agents and lornoxicam. These pellets were left uncoated or were coated with hydroxypropylmethylcellulose (inner coat, outer coat). A mixture of quick release granulate and a delayed release fraction of coated pellet cores were filled in a final unit dosage form.

In D2 a solid pharmaceutical dosage was described which comprises benzimidazole proton pump inhibitors, a primary essential buffer and an optional secondary essential buffer (such as sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, aluminium hydroxide, phosphate derivatives, calcium hydroxide). The two-part tablets provide an inner core with proton pump inhibitors and a primary essential buffer (sodium bicarbonate) and in addition an outer phase with sodium bicarbonate.

D3 discloses two-part tablets comprising a) a core containing omeprazole and sodium bicarbonate/calcium hydroxide and b) an outer phase containing calcium carbonate for the manufacture of a medicament for treating gastric acid disorders.

Solid pharmaceutical dosage forms (tablets, capsules, caplets) are described in D4. These compositions comprise at least one PPI, at least one buffering agent (sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, aluminium hydroxide, sodium carbonate, magnesium hydroxide, phosphate derivatives) and optionally one or more excipients and are used for the manufacture of a medicament for treating gastrointestinal disorders.

2.2) D1-D4 do not disclose compositions of at least three multiple unit populations which comprise a) multiple units for the initial dose of the active principle of a proton pump inhibitor, b) multiple units of a basic agent and c) multiple units for a delayed release of said active principle.
In addition, D1-D4 do not disclose beads/pellets/tablets/granules in a composition comprising a) a population of a pharmaceutical active , b) a population of a basic substance, c) a population of an enteric-coated pharmaceutical active and d) a population of an enteric coated basic substance.

2.3) In the light of D1 -D4 (see sections V-1, 2.1, 2.2) and under consideration of section III- 1., the subject-matter of claims 1-48 is considered novel according to Article 33 (1) and (2) PCT, since its corresponding content is not disclosed by D1-D4.

3) Inventive Step - Article 33 (1) and (3) PCT

3.1) The problem posed in the present application was the development of a composition comprising a proton type inhibitor attaining full inhibition of acid secretion, being chemically stable and ensuring a more precise drug release.

The solution according to the Applicant was an oral pharmaceutical composition comprising multiple populations of at least one of beads, pellets, tablets and granules provided in a capsule, the composition comprising:

- a first population of a pharmaceutical active comprising a pharmaceutical active substance releasable at a first rate (preferable PPI)
- a population of a basic substance
- a second population of a pharmaceutical active comprising a pharmaceutical active substance releasable at a second rate (here also with enteric coating or with a separating layer and an enteric coating optionally)
- a population of a basic substance, wherin the basic substance is released slower than the basic substance of b) (here also with enteric coating or with a separating layer and an enteric coating).

D1 which is regarded closest prior art discloses an oral pharmaceutical composition based on modified release multiple units (such as pellets) which are packed in a unit dosage form. This composition comprises:

- a first NSAID-containing fraction of multiple units for quick release of the NSAID
- a second NSAID-containing fraction of multiple units in the form of coated delayed release multiple units. Proton pump inhibitors are listed as further active drug substances.

In the examples 7-9 pellet cores were manufactured which comprised sodium bicarbonate, dibasic calcium phosphate as alkaline agents and lornoxicam. These pellets were left uncoated or coated with hydroxypropylmethylcellulose (inner coat, outer coat). A mixture of quick release granulate and

a delayed release fraction of coated pellet cores were filled in a final unit dosage form. Besides NSAIDs proton pump inhibitors can be chosen as active agents in the same delayed-release composition.

D1 does not disclose separate multiple units comprising a basic substance.

It appears to be obvious to a person skilled in the art to derive compositions where the basic substances are put in separate pellets besides those pellets for different release pattern for the active principle. Proton pump inhibitors are - for reasons of stability - characteristically packed in compositions together with a basic agent. This can also be recognized from D2-D4.

Unexpected or surprising effects have not been demonstrated for the separate use of pellets containing basic substances besides those containing the proton pump inhibitor in comparison to the combined use of proton pump inhibitors and basic agents in the multiple unit.

3.2) Therefore, under provision of III-1., the subject-matter of claims 1-48 is obvious to a person skilled in the art due to general textbook knowledge about compositions of proton pump inhibitors and due to common experience. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

4) Industrial Applicability

For the assessment of the present claims 29, 30, 46-48 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5) Further remarks

The Applicant's attention is drawn to the fact that the application must not be altered thus that its subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).